REMARKS

Claims 1, 15, 16, 26 and 28 have been amended. New Claims 29-30 have been added. Accordingly, claims 1-21 and 25-30 are pending. Support for the amendment and new claims is found throughout the specification and claims as originally filed. For example, the amendments are supported by the specification at page 9, lines 8-12 and page 10, lines 14-20. New Claims 29-30 are supported by the specification at page 21, line 6 through page 22, line 3. Accordingly, no new matter has been added.

In response to the Office Action mailed on December 16, 2010, Applicants submit the following remarks.

Interview

Applicants wish to thank the Examiners for their time during the interview held on June 7, 2011.

Rejection of Claims 1-8, 10, 11, 14-19, 21 and 25-28 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-8, 10, 11, 14-19, 21 and 25-28 under 35 U.S.C. §103(a) as allegedly being unpatentable over Forster et al. (AU52162/96, hereinafter "Forster") in as evidenced by Lau et al. (WO 2004/069242, hereinafter "Lau") view of Ludwig et al (U.S. 4,331,652, hereinafter "Ludwig"). Specifically, the Examiner asserts Forster teaches combinations of anthelmintics. The Examiner acknowledges that Forster does not teach an intraruminal bolus device, stepwise method or efficacy duration. However, the Examiner alleges that such features are taught by Ludwig. The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art to utilize the composition of Forster in combination with the continuous release allegedly taught by Ludwig.

Applicants note that, as amended, the present claims relate to a controlled release device that delivers the equivalent of a high dose every day for a period of at least 3 days and no more than 6 to 8 days, a time period that is long enough to provide extremely high efficacy against parasites, but not long enough to cause toxicity to the animal or build up resistance in worm populations. Specification at page 13, lines 19-23. Thus, a key advantage of the claimed methods is that the combined force of multiple anthelmintics at high dosage achieves high

efficacy against resistant genotypes in order to delay development of resistant populations. This effect is achieved by delivering the multiple anthelmintics in the form of a bolus which is targeted towards and remains within the rumen of the animal. Specification at page 14, lines 9-12. Accordingly, Applicants submit that the instant claims are not obvious for the following reasons.

1. The prior art references, either alone or when combined, fail to teach or suggest all of the elements of independent Claims 1 or 26.

The law dictates that in order to establish a *prima facie* case of obviousness, among other things, the prior art must teach or suggest all the claim limitations. (M.P.E.P. § 2143).

Forster and Ludwig, either alone or when combined, fail to teach or suggest all of the elements of independent Claims 1 or 26 as amended, or any of the claims dependent thereon. Specifically, neither Forster nor Ludwig teach or suggest "introducing to the ruminant animal a single delivery device comprising said two or more anthelmintic compounds of differing chemical groups; wherein said delivery device is an intra-ruminal bolus configured to release from the rumen said effective daily dose each day for said duration of exposure, wherein said duration of exposure comprises at least 3 days and no more than 6 to 8 days," as recited in amended Claim 1. Similarly, none of the cited references, alone or combined, teach "a defined period of between 3 and 8 days, and wherein said delivery device is configured to terminate release by the end of said defined period.

Duration of exposure. The Examiner concedes that Forster does not teach efficacy duration, and asserts that Ludwig teaches protection against parasites for a predetermined period of time, such as about 10 to about 60 days. Although Applicants maintain that neither Forster nor Ludwig disclose the claimed subject matter, solely in an effort to expedite prosecution, Applicants have amended Claims 1 to recite a duration of exposure of "at least 3 days and no more than 6 to 8 days." Similarly, Applicants have amended Claim 26 to recite "a defined period of between 3 and 8 days, and wherein said delivery device is configured to terminate release by the end of said defined period." Accordingly, Applicants submit that neither Forster nor Ludwig disclose a duration of exposure that comprises at least 3 days and no more than 6 to 8 days. Ludwig relates to controlled release formulations containing a single active agent, and discloses

payout periods of 10 to 60 days, and typically about 30 days. Ludwig at column 6, lines 37-39. In fact, the *in vivo* experiments disclosed by Ludwig involve treatment periods ranging from 28 days to 70 days. Ludwig at Tables I and II. In contrast, amended Claim 1 recites, in relevant part, a duration of exposure of "at least 3 days and no more than 6 to 8 days." Because Ludwig teaches a duration of exposure from 10 to about 60 days, Ludwig fails to disclose a duration of exposure of at least 3 days and no more than 6 to 8 days as recited in amended Claims 1 or 26. Because Ludwig does not disclose this element, Ludwig fails to teach, suggest or in any way make obvious each of the elements of amended Claims 1 and 26.

Effective daily dose. The Examiner asserts that the anthelmintic preparation of Forster would have been active against parasites in ruminant animals such as sheep. In support of this assertion, the Examiner cites to a non-prior art reference (Lau) and states that Lau provides evidence that the anthelmintic preparation of Forster demonstrate reduction of parasite burden in sheep. Office Action at page 6. Although Applicants maintain that neither Forster nor Ludwig disclose the claimed subject matter, solely in an effort to expedite prosecution, Applicants have amended Claim 1 to recite, in relevant part, "providing an effective daily dose for each of at least two anthelmintic compounds of differing chemical groups, wherein said effective daily dose is sufficient to effect a reduction in the level of resistant parasites in a ruminant animal." Accordingly, Applicants submit that neither Forster nor Ludwig disclose treating resistant parasites in ruminant animals.

Forster relates to preparations of anthelmintics for treatment of worms in dogs. Specifically, Forster focuses on canine administration of low-dose abamectin in combination with a benzimadazoles such as oxibendazole. Forster at page 3, first paragraph. The Examiner points to a non-prior art reference (Lau) as evidence that the canine preparation of Forster would be effective in sheep. However, Lau fails to provide such evidence. First, the formulations of Lau include a combination of four different anthelmintic agents, rather than the two-agent formulation of Forster. Lau at pages 7-10. Second, the formulations of Lau contain doses of abamectin (200 μg/kg) that are more than ten time higher than those disclosed by Forster (15 μg/kg). Lau at Table 3. Accordingly, there is nothing in the disclosure of Lau that would indicate that the doses of abamectin disclosed by Forster would be effective in sheep. As such, Forster fails to teach "providing an effective daily dose for each of at least two anthelmintic

compounds of differing chemical groups, wherein said effective daily dose is sufficient to effect a reduction in the level of resistant parasites in a ruminant animal," as recited in amended Claim 1.

Ludwig does not remedy this deficiency. In fact, the disclosure of Ludwig is silent regarding resistant parasites. Additionally, the discussion of dosages in Ludwig is specific to a single class of anthelmintics: benzimidazoles. Ludwig at column 7, lines 39-51. As such, the disclosure of Ludwig fails to teach "providing an effective daily dose for each of at least two anthelmintic compounds of differing chemical groups, wherein said effective daily dose is sufficient to effect a reduction in the level of resistant parasites in a ruminant animal," as recited in amended Claim 1.

Accordingly, even when combined, none of the cited references, alone or combined, teaches all of the elements of the claimed invention, including "providing an effective daily dose for each of at least two anthelmintic compounds of differing chemical groups, wherein said effective daily dose is sufficient to effect a reduction in the level of resistant parasites in a ruminant animal," as recited in Claim 1 as amended. Because the cited references fail to teach each and every element of Claim 1, a *prima facie* case of obviousness has not been established.

2. The proposed combination would render Forster unsatisfactory for its intended purpose.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). As discussed below, the proposed combination of Ludwig and Forster would render Forster inoperable and/or unsatisfactory for its intended purpose.

Forster. The stated purpose of Forster is "to provide a broad spectrum worming preparation for dogs which utilizes a synergistic effect observed for administration of abamectin in dosages of less than 15 μg per kilogram of animal body weight in combination with oxibendzole." Forster at page 3, first paragraph. Forster also teaches that the chewable tablet preparations are advantageous for administration once each six weeks. Forster at page 5.

Ludwig. In contrast, Ludwig discloses controlled-release polymers for use in ruminant animals such as sheep. In particular, Ludwig teaches that the formulation is encapsulated in steel

cylinders that are of sufficient density to remain indefinitely in the reticulo-rumen of the ruminant. For this reason, Ludwig teaches that the device "is ideally suited to use in feed lots as well as to use in range fed animals." Ludwig at column 7, lines 65-67. In particular, Ludwig states: "[o]nce all of the formulation contained in the steel capsule has been released, the empty capsule is of such weight that is simply remains in the reticulorumen. Additional filled capsules can be administered as needed, and all such capsules can be removed at the time of slaughter." Ludwig at column 9, lines 29-34. Additionally, Ludwig teaches that the effective dose of anthelmintic to be administered amounts to "no less than 500 mg per animal each day." Ludwig at column 6, lines 35-37.

The Examiner asserts that one of skill in the art would have been motivated to use the bolus device of Ludwig to administer the compositions of Forster. Office Action at page 7. The Examiner first asserts that an ordinary artisan would have been motivated to do so because Lau teaches formulations and dosages for sheep. Office Action at page 6. The Examiner next asserts that an ordinary artisan would have been motivated by the stated benefits of Ludwig which include the lack of undesired chemical residues used in animals for human food production. Office Action at page 7. Applicants disagree, and maintain that the combination of Forster with Ludwig would render the combination inoperable or unsatisfactory for the intended purpose of Forster. The combination is problematic in several aspects, each of which is discussed further below.

First, the ruminal bolus device of Ludwig would not be suitable for use in a dog. Dogs lack a rumen, and therefore the bolus device of Ludwig would not persist in the animal's gastrointestinal system as it would in a sheep or cow. Even if steel canisters did persist in a dog, the use of multiple steel canisters until the time of slaughter, as taught by Ludwig, would be inconsistent with the chewable dog tablets which are designed to allow long-term repeated dosing at six-week intervals. As such, the proposed modification renders the resulting combination unsatisfactory for the intended purpose of Forster.

Applicants note that the Examiner points to Lau and asserts that Lau "establishes a reasonable expectation of success" that the canine compositions of Forster would have been suitable in sheep. Office Action at page 6. However, Applicants respectfully point out that Lau is not prior art. One of skill in the art at the time the instant application was filed would not have

been aware of the teachings of Lau. Therefore, contrary to the assertions of the Examiner, Lau could not have provided any expectation that the canine compositions of Forster would have been effective in sheep.

Second, the daily dose of anthelmintic taught by Ludwig is inconsistent with doses of abamectin in dogs as taught by Forster. Specifically, Ludwig teaches that the effective dose of anthelmintic to be administered amounts to "no less than 500 mg per animal each day." Ludwig at column 6, lines 35-37. Thus, if abamectin were administered using the proposed dose of Ludwig to a typical dog weighing between 1 to 50 kg, the resulting dose would be between 10 mg and 500 mg per kilogram. This resulting dose is between six hundred to thirty thousand times greater than the "less than 15 μg per kilogram" abamectin dose that Forster aspires to achieve in dogs. As such, the proposed modification renders the resulting combination inoperable for the intended purpose of Forster.

For at least the reasons provided above, the combination of Forster and Ludwig results in a method that would be inoperable for the intended purpose of treating dogs with low doses of abamectin as set forth in Forster. Accordingly, there is no suggestion or motivation to make the proposed modification to Forster, and the claimed combination would therefore not have been obvious to one of skill in the art at the time the instant application was filed.

3. Applicants' evidence of unexpected advantages rebut any *prima facie* case by the Examiner

Evidence of unobvious or unexpected advantageous properties can rebut *prima facie* obviousness. *See* MPEP §§ 716.02(a) and 2144.09.

In addition to the above, Applicants submit that *even if* the claimed methods were considered *prima facie* obvious, the instant specification provides evidence of the surprising effectiveness of the claimed methods in treating resistant strains of parasites. Specifically, the specification describes the unexpected finding that high doses of two or more anthelmintic compounds of different chemical groups can be used in combination over a limited duration of exposure to effectively eliminate resistant parasite strains. The specification sets forth the results of a variety of studies to test the efficacy of the claimed methods. The results from these studies

were unexpected in view of the prior art, and show robust effects in treating resistant parasite strains in sheep and cattle, as discussed below.

At the time the instant application was filed, it was known that prolonged delivery of small doses of anthelmintic had limited efficacy and were often no better than a single oral dose. Specification at page 4, lines 3-22. Further, it was known that prolonged delivery of small doses may actually select for resistance in the worm population. Specification at page 5, lines 3-7. Thus, as more fully discussed below, it was surprisingly and unexpectedly discovered by the inventors of the claimed methods, that controlled release of high doses of multiple anthelmintic classes over a prolonged duration was able to control resistant parasite strains with vastly improved efficacy.

Trials 1 and 2 provided an initial proof of concept of the surprising nature of the claimed method. For example, when compared with a single dose of moxidectin, which was recognized as the most potent single active product on the market, a seven-day exposure to high doses of abamectin demonstrated superior effectiveness against abamectin-resistant parasites in lambs. See Table 2. Further, as shown in Table 2, administration of a 0.18 mg/kg daily dose of abamectin for 7 days resulted in a 96.4%, reduction in worm count for abamectin-resistant *Ostertagia cicumcincta*, which is an efficacy that is more than double that of a single administration of a higher dose of abamectin. These results show the surprising effectiveness of administration of a high dose over a 7 day period, and provided the basis for additional studies set forth in the specification.

Trials 3 and 4 were conducted to test bolus formulations designed to deliver high doses of albendazole and abamectin over an extended duration of exposure. As shown in Tables 3 and 4, these results demonstrate that against a range of resistant parasites, extending the duration of exposure using a bolus dose was as good as and often far superior to administering a single dose. These results also demonstrate that keeping the daily dose rate as high as possible proved to be most effective.

When these high doses of abamectin and albendazole were combined in a bolus for extended delivery, the results were surprisingly superior to various single administrations. Table 5 shows that prolonged administration of a 0.18 mg/kg dose of abamectin and 5mg/kg dose of albendazole resulted in a 99.1% and 100% reduction in multiple drug resistant *Ostertagia*

circumcincta and *Trichostrongylus colubriformis*, respectively. This efficacy is striking in comparison to a single oral dose of the same compounds, and compared to a single oral dose of moxidectin, which was recognized as the most potent single active product on the market. Specification at page 22, lines 1-3.

Further, one of skill in the art would have been concerned with the potential for toxicity when using two anthelmintics in combination at high doses and for a prolonged period. Specification at page 9, lines 10-12, 21-24, and page 10, lines 14-17. Therefore, it was surprising that a daily dose of 3-5 mg/kg/day of albendazole, delivered with 0.1-0.2 mg/kg/day of abamectin over a prolonged period, was well tolerated by the animals.

Thus, the compelling results of the claimed methods in treating resistant strains of parasites are further evidence that the claimed methods were surprising and unexpected, and would not have been obvious to one of skill in the art. Nothing in the prior art cited by the Examiner, and nothing within the knowledge of those having skill in the art would have led one of skill in the art to the claimed methods.

Taken together, this evidence rebuts any *prima facie* case of obviousness by the Examiner. Accordingly, Applicants submit that Claims 1-8, 10, 11, 14-19, 21 and 25-28 are not obvious under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Rejection of Claim 20 under 35 U.S.C. § 103(a)

The Examiner rejects Claim 20 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Forster as evidenced by Lau and in view of Ludwig, and further in view of Whitehead (U.S. 6,030,637, hereinafter "Whitehead"). Specifically, the Examiner rejects Claim 20, alleging that although Forster or Ludwig do not teach the recited features, such features are taught by Whitehead. Specifically, the Examiner alleges that Whitehead teaches a maximum integral dose. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art to utilize the anthelmintic compositions of Forster and Ludwig in combination with the features allegedly taught by Whitehead. Applicants disagree.

Claim 20 depends from independent Claim 1. As discussed previously, none of Forster or Ludwig, either alone or in combination, teach or suggest all the limitations of Claim 1 as amended. Whitehead fails to remedy that deficiency. Specifically, Whitehead fails to teach or suggest "introducing to the ruminant animal a single delivery device comprising said two or more anthelmintic compounds of differing chemical groups; wherein said delivery device is an intra-ruminal bolus configured to release from the rumen said effective daily dose each day for said duration of exposure, wherein said duration of exposure comprises at least 3 days and no more than 6 to 8 days," as recited in amended Claim 1. Because Whitehead fails to teach this missing element, Whitehead fails to teach or suggest all of the claim limitations. Accordingly, for at least this reason, a *prima facie* case of obviousness has not been established for dependent Claim 20.

Applicants therefore submit that Claim 20 is not obvious under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Rejection of Claim 12 under 35 U.S.C. § 103(a)

The Examiner rejects Claim 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Forster as evidenced by Lau and in view of Ludwig, and further in view of IVS Annual Index of Veterinary Products (hereinafter "IVS"). Specifically, the Examiner asserts that although Forster and Ludwig do not teach the dosage of albendazole recited in claim 12, such dose range is taught by IVS. The Examiner then concludes that the dosage quantity disclosed by IVS would have rendered the claimed dose range obvious. Applicants disagree.

Applicant maintains that Claim 12 is not obvious over Forster as evidenced by Lau and in view of Ludwig, and further in view of IVS because none of these references, either alone or combined, teach or suggest all the limitations of the rejected claim. Claim 12 depends from Claim 11, which depends from Claim 10, which depends from independent Claim 1. As discussed above in the response to the rejection of Claims 1-8, 10, 11, 14-19, 21 and 25-28 under 35 U.S.C. § 103(a), Forster and Ludwig fail to teach "introducing to the ruminant animal a single delivery device comprising said two or more anthelmintic compounds of differing chemical groups; wherein said delivery device is an intra-ruminal bolus configured to release from the rumen said effective daily dose each day for said duration of exposure, wherein said duration of exposure comprises at least 3 days and no more than 6 to 8 days," as recited in amended Claim 1.

Applicant respectfully submits that IVS fails to remedy this defect. At best, IVS teaches an effective dosage for a single anthelmintic agent. However, IVS fails to teach the duration of exposure recited in claim 1 as amended. Because IVS fails to teach this missing feature, IVS fails to teach or suggest all of the claim limitations. Accordingly, for at least this reason, a *prima facie* case of obviousness has not been established for Claim 12.

Applicants therefore submit that Claim 12 is not obvious under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Rejection of Claim 13 under 35 U.S.C. § 103(a)

The Examiner rejects Claim 13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Forster as evidenced by Lau and in view of Ludwig, and further in view of Sanyal (Vet. Res. Comm. 20, 1996, 461-468, hereinafter "Sanyal"). Specifically, the Examiner asserts that although Forster and Ludwig do not teach the use of tricalbendazole, such use is taught by Sanyal as a low-level intraruminal anti-fluke agent. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art to use triclabendazole disclosed by Sanyal in the bolus of Ludwig. Applicants disagree.

Applicant maintains that Claim 13 is not obvious over Forster in view of Ludwig as and further in view of Sanyal because neither of these references, either alone or combined, teach or suggest all the limitations of the rejected claim. Claim 13 depends from independent Claim 1. As discussed above in the response to the rejection of Claims 1-8, 10, 11, 14-19, 21 and 25-28 under 35 U.S.C. § 103(a), Forster and Ludwig fail to teach "introducing to the ruminant animal a single delivery device comprising said two or more anthelmintic compounds of differing chemical groups; wherein said delivery device is an intra-ruminal bolus configured to release from the rumen said effective daily dose each day for said duration of exposure, wherein said duration of exposure comprises at least 3 days and no more than 6 to 8 days," as recited in amended Claim 1. Applicant respectfully submits that Sanyal fails to remedy this defect. At best, Sanyal teaches use of triclabendazole as an anthelmintic agent. However, Sanyal fails to teach the duration of exposure recited in claim 1 as amended. Because Sanyal fails to teach this missing feature, Sanyal fails to teach or suggest all of the claim limitations. Accordingly, for at least this reason, a *prima facie* case of obviousness has not been established for Claim 13.

Applicants therefore submit that Claim 13 is not obvious under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Rejection of Claim 9 under 35 U.S.C. § 103(a)

The Examiner rejects Claim 9 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Forster as evidenced by Lau and in view of Ludwig, and further in view of Jeannin et al. (U.S. 6,162,820, hereinafter "Jeannin"). Specifically, the Examiner asserts that although Forster and Ludwig do not teach the abamectin dosage recited in Claim 9, such dosages are taught by Jeannin. The Examiner then concludes that one of ordinary skill in the art would have expected reasonable success from using abamectin in the range disclosed by Jeannin. Applicants disagree.

Applicant maintains that Claim 9 is not obvious over Forster in view of Ludwig as and further in view of Jeannin because none of these references, either alone or combined, teach or suggest all the limitations of the rejected claim. Claim 9 depends indirectly from independent Claim 1. As discussed above in the response to the rejection of Claims 1-8, 10, 11, 14-19, 21 and 25-28 under 35 U.S.C. § 103(a), Forster and Ludwig fail to teach "introducing to the ruminant animal a single delivery device comprising said two or more anthelmintic compounds of differing chemical groups; wherein said delivery device is an intra-ruminal bolus configured to release from the rumen said effective daily dose each day for said duration of exposure, wherein said duration of exposure comprises at least 3 days and no more than 6 to 8 days," as recited in amended Claim 1. The disclosure of Jeannin fails to remedy this deficiency. Because Jeannin fails to teach this missing feature, Jeannin fails to teach or suggest all of the claim limitations. Accordingly, for at least this reason, a *prima facie* case of obviousness has not been established for Claim 9.

Applicants therefore submit that Claim 9 is not obvious under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of this rejection and allowance of the pending claims.

Double Patenting

The Examiner provisionally rejects claims 1, 3, 15 and 16 on the ground of nonstatutory double patenting over claims 1-4 and 20 of copending Application No. 11/908,708. Applicants

will consider submitting a terminal disclaimer to overcome the rejection of Claims 1, 3, 15 and 16 once claims 1, 3, 15 and 16 of the instant application are found to be otherwise allowable.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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